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Systematic review and meta-analysis: high mortality in patients with non-severe alcoholic hepatitis

Short title: Mortality of non-severe alcoholic hepatitis

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Abstract

Background

Alcoholic hepatitis is a serious complication of alcohol misuse. Severe alcoholic hepatitis with its high mortality, has been investigated in detail but 'non-severe alcoholic hepatitis' is poorly characterised. Survival of this group of patients is unknown.

Aim

To conduct a systematic review and meta-analysis to determine 28-day, 90-day and 1-year mortality of patients with non-severe alcoholic hepatitis.

Methods

The protocol was registered on the PROSPERO database (CRD42018107451). Embase, Medline and Cochrane Central databases were searched until July 2018. All study designs reporting mortality rates in patients with non-severe alcoholic hepatitis were eligible. Mortality data were extracted and meta-analysis performed using a random effects model. Risk of bias was assessed by Cochrane risk of bias or National Institutes of Health quality assessment tool for case series studies.

Results

Twenty-five studies (n=1372 patients; 12 prospective) met criteria. Twenty-eight day mortality (17 studies; n=993) was 6% (95% CI 3-9%; I^2=67.3%; p<0.001), 90-day mortality (15 studies; n=755) was 7% (4-11%, I^2=64.2%; p<0.001) and 1-year mortality (five studies; n=234) was 13% (4-24%; I^2=72%; p=0.006). Subgroup analyses by method of diagnosis (histological versus clinical) or study design (prospective versus retrospective) did not reveal differences in mortality.

Conclusion

Non-severe alcoholic hepatitis is not benign with 6% and 13% 28-day and 1-year mortality, respectively. This systematic review demonstrates the paucity of high quality studies in patients with non-severe alcoholic hepatitis. Our analysis suggests that patients who do not meet criteria for severe alcoholic hepatitis are an important and hitherto overlooked clinical group. Full characterisation of clinical outcome and development of treatment strategies to reduce mortality in this group is a priority.

Keywords

Alcoholic hepatitis, mortality, systematic review, meta-analysis

Background

Alcoholic hepatitis is a serious complication of alcohol-related liver disease characterised by recent onset jaundice and coagulopathy in heavy long-term alcohol consumers.[1] Its incidence in Europe is increasing[2, 3] and it accounts for approximately 0.7% of unplanned hospital admissions in USA.[4]

Analysis of the seminal randomised controlled trial (RCT) of corticosteroids by Maddrey in 1978[5] determined that corticosteroid treatment was of most benefit in the 15 patients with severe disease defined by a discriminant function (DF) based on bilirubin and prothrombin time with a threshold of 93. All 40 patients with DF < 93 survived. The threshold was subsequently modified to 32 to take into account inter-laboratory variation in prothrombin time measurement.[6] It has since been assumed that patients with DF < 32 have a good prognosis. This threshold has been applied to classify severe disease and has been adopted both in clinical guidelines as a treatment trigger[7, 8] and as a clinical trial inclusion criterion.[9] A recent expert review has recognised that the prognosis of these patients may not be as good as previously believed and recommends studies to define the natural history and outcome of patients with non-severe alcoholic hepatitis.[10]

In an attempt to better identify alcoholic hepatitis patients at highest risk of death, other severity scores have been derived from cohort studies including the Glasgow Alcoholic Hepatitis Score (GAHS),[11] Model for End-stage Liver Disease (MELD)[12] and Age Bilirubin Creatinine INR (ABIC).[13] A GAHS threshold of nine had low sensitivity (54% and 43% at 28- and 84-days, respectively) but high specificity (89% and 90% at 28- and 84-days, respectively) in predicting mortality.[11] A MELD score of > 21 had both sensitivity and specificity of 75% in predicting 90-day mortality.[12] Two thresholds were applied to the ABIC

score; patients with ABIC > 9.0 had 75% risk of death at 90-days compared to 30% with ABIC 6.71-9.0 and 0% with ABIC < 6.71.[13] Application and comparison of these scores to independent cohorts has demonstrated similar predictive accuracy to the DF for early mortality.[14-16] However, no score is accurate in identifying alcoholic hepatitis patients with the lowest risk of mortality (non-severe alcoholic hepatitis). Even patients classified by ABIC < 6.71 have up to 11% 28-day mortality when applied to an independent cohort.[17]

Over the last 4 decades, a significant body of literature has been amassed on severe alcoholic hepatitis with clearly defined clinical characteristics and short- and medium-term survival.[18, 19] The most recent individual patient data meta-analysis from 11 RCTs including over 2,000 patients described a 19% and 38% mortality at 28 days and 6 months respectively.[20] Mortality at 1 year was 56% in the largest RCT performed [21] and causes of death are well documented.[19, 21] In contrast, little is known about the characteristics and outcome of patients with less severe alcoholic hepatitis, so called 'non-severe alcoholic hepatitis', which has been assumed a relatively benign condition with low risk of mortality.

The incidence of non-severe alcoholic hepatitis is uncertain but it is likely that non-severe alcoholic hepatitis is more common than its severe form. This is supported by data from the STOPAH RCT of prednisolone and pentoxifylline in severe alcoholic hepatitis (DF ≥ 32), in which 1103 of 3109 patients with a clinical diagnosis of alcoholic hepatitis who were screened met inclusion criteria and were randomised. 2006 screen failures did not meet inclusion criteria due to milder disease (DF < 32 or bilirubin < 80 μmol/L).[21]

The aim of this study was to perform a systematic review and meta-analysis of observational studies and clinical trials to determine short (28- and 90-day) and medium (1-year) term mortality of patients with non-severe alcoholic hepatitis.

Methods

Data sources and searches

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses and registered prospectively on the PROSPERO database (ID: CRD42018107451). PubMed MEDLINE (1946-2018), EMBASE (1974-2018) and Cochrane CENTRAL databases were searched. Abstracts from international liver conferences (EASL, AASLD, APASL and DDW) were also searched from 1985 onwards and reference lists of included studies were reviewed.

For CENTRAL, the single search term of “alcoholic hepatitis” in title, abstract or keyword was used. For MEDLINE, the following keywords were used with (“hepatitis, alcoholic”[MeSH Terms] OR (“alcoholic hepatitis”[All Fields])): “mortality”, “survival”, “prognosis”, “biomarker” and “outcome”. For EMBASE: “alcoholic hepatitis”[All fields] and the keywords “mortality”, “survival”, “prognosis”, “biomarker” and “outcome”. The term “biomarker” was included to ensure all studies of clinical biomarkers in non-severe alcoholic hepatitis were included. The full search strategy is presented in the supplementary materials.

Study selection

The population of interest was all alcoholic hepatitis and the primary outcome was mortality. Alcoholic hepatitis was defined either by characteristic histological features on liver biopsy or by clinical characteristics. Studies that reported histological confirmation of alcoholic hepatitis in fewer than half of participants were classified as using a clinical definition of alcoholic hepatitis. Studies were included if they reported 28-day, 90-day or 1-year mortality after diagnosis for patients with non-severe alcoholic hepatitis. Reports in any language were eligible and foreign texts were translated using online translation tools. All study designs were eligible including retrospective or prospective observational studies, RCTs or

non-randomised clinical trials. Non-severe alcoholic hepatitis was defined as DF < 32, MELD < 21,[12] ABIC < 6.71[13] or bilirubin < 85 μmol/L with histological confirmation.

Data extraction and management

Two reviewers (AD and KB) independently performed the searches and identified relevant papers by review of titles and abstracts. Results were collated and inconsistencies resolved by a third reviewer (MC). Information on study design, ethnicity, intervention, definition of non-severe alcoholic hepatitis, causes of death and mortality rate at 28 days, 90 days and 1 year were extracted into pre-piloted forms. In RCTs, mortality in control and intervention groups were combined. In papers reporting the same cohort of patients, only the most recent report was included. Where outcomes for non-severe alcoholic hepatitis patients were reported only in combination with severe alcoholic hepatitis patients, the corresponding author of the report was contacted by email on one occasion to provide additional data where possible. If no response was obtained, the study was excluded from the analysis.

Risk of bias assessment

For RCTs, the risk of bias was assessed using the Cochrane risk of bias tool for RCTs[22]. As mortality rates from each arm were pooled, criteria for ramdomisation method, allocation method and blinding were not relevant to assess. Each study was assessed as being of high, unclear or low risk of bias. For cohort studies, the National Institutes of Health quality assessment tool for case series studies[23] was chosen as most risk of bias domains validated for cohort studies do not apply to this review, which extracted data from patients with non-severe alcoholic hepatitis from larger cohort studies. The quality of each study was rated as poor, fair or good.

Data synthesis and analysis

For each study, the proportion of non-severe alcoholic hepatitis who had died up to a specific time point (28 days, 90 days or 1 year) was given by the number of people dying up

to that time point divided by the total number of people diagnosed with non-severe alcoholic hepatitis. Individual study results were combined using a random-effects model.[24] The overall proportion is a weighted mean where the weight assigned to each study is the inverse of the study's variance. The pooled estimate is calculated after Freeman-Tukey double arcsine transformation to stabilise the variances.[25] Forest plots of proportions along with their 95% confidence intervals were produced for each study and for the overall result. We assessed heterogeneity between studies by using I^2 test statistic[26] and small study effects using Egger's test.[27] Substantial heterogeneity was considered to be present if I^2 was 50-90%. Egger's test was not applied to meta-analyses of less than 10 studies.

Data analysis was conducted using Stata 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The Metaprop Stata package was used to generate the forest plots.[28]

Subgroup analyses

No pre-specified subgroup analyses were defined. However, the method of classification of non-severe alcoholic hepatitis may define different groups of patients.[29] A sensitivity analysis excluding studies using classifications other than DF < 32 was performed. Non-severe alcoholic hepatitis may be challenging to diagnose on clinical grounds alone and overlaps with decompensated chronic alcohol-related liver disease. Therefore, a subgroup analysis was performed to determine whether the method of diagnosis of alcoholic hepatitis (clinical versus histological) influenced reported mortality. Furthermore, the National Institute of Alcoholism and Alcohol Abuse (NIAAA) recently developed well-defined patient selection criteria for alcoholic hepatitis studies.[9] "Definite" alcoholic hepatitis is clinically diagnosed and biopsy proven. "Probable" alcoholic hepatitis has a 90% specificity when defined as: 1) alcohol consumption > 40 g/day (females) and > 60 g/day (males) for more than 6 months with less than 60 days abstinence before onset of jaundice; 2) onset of jaundice within prior 8 weeks; 3) AST:ALT > 1.5 and both ALT and AST < 400 IU/L; 4) serum bilirubin > 51

μmol/L (3 mg/dL). We conducted a subgroup analysis to determine whether mortality differed in studies that included patients with the NIAAA definition of definite or probable alcoholic hepatitis compared to other studies.

Retrospective observational studies are prone to bias due to the method of case finding. To investigate the effect of study design, an additional comparison of mortality proportions was made between prospective and retrospective studies. Studies conducted in patients with severe alcoholic hepatitis from non-Caucasian populations have reported high mortality of over 50% at 90 days.[30, 31] Therefore, a subgroup analysis to determine the influence of ethnicity on mortality proportion was performed. A final subgroup analysis was performed to evaluate whether mortality proportion differed in studies published in or prior to 2010 compared to those published after 2010.

Results

The search strategy identified 2568 unique records. After review of titles and abstracts, 71 records were relevant and full text manuscripts were obtained and reviewed. Survival data for patients with non-severe alcoholic hepatitis were reported in 25 manuscripts (figure 1).[5, 11, 14, 15, 32-52] Additional data from a further four studies were requested by email from the corresponding authors. One response was received but no additional data were available for that study. Individual study details are outlined in Table S2.

Mortality

The crude mortality rates of patients with non-severe alcoholic hepatitis was 76/993 (7.6%) within 28 days, 75/755 (9.9%) within 90 days and 38/234 (16.2%) within one year. Seventeen studies reported the proportion of patients with non-severe alcoholic hepatitis

dying within 28-days with estimated mortality in 993 patients of 6% (95% confidence interval 3-9%; I^2=67.3%; p<0.001; figure 2). Fifteen studies in a total of 755 patients reported 90-day mortality with overall estimated mortality of 7% (4-11%; I^2=64.2%; p<0.001; figure 3). Five studies reported the proportion of patients with non-severe alcoholic hepatitis dying within 1 year. Overall estimated mortality in 234 patients was 13% (4-24%; I^2=72%; p=0.006; figure 4). Substantial heterogeneity was seen in all analyses.

Cause of death

Three studies specifically reported cause of death in patients with non-severe alcoholic hepatitis.[39, 44, 45] Of the 13 deaths within one year reported in these studies, eight (62%) were liver related, one (8%) due to sepsis and four (30%) due to other causes. The remaining studies did not report cause of death or combined all patients with alcoholic hepatitis, including severe alcoholic hepatitis.

Study and participant characteristics

All studies reported the source of data and study design. Gender and age range was missing from 76% (19/25) of studies and severity of alcoholic hepatitis (baseline bilirubin, DF, ABIC or MELD score) was missing from 80% (20/25) of studies. Multivariable meta-regression was not performed given the limited data. Mean or median DF was reported in five studies and ranged from 12 to 20 with individual scores between 0.3 and 31 (supplementary table 2). Mean or median bilirubin was reported in five studies and ranged from 26 to 140 µmol/L with individual values between 3 and 393 µmol/L (supplementary table 2).

Study type and risk of bias assessment

Of the 25 included studies, 12 were prospective and 13 retrospective in design. Four were RCTs of amlodipine,[34] corticosteroids,[5] vitamin E[45] and corticosteroids with oxandrolone.[43] There was one open-label clinical trial of etanercept.[44] Median study population size was 46 (range 3 – 172). Egger's test of bias from small study effect was not statistically significant

for any analysis (p=0.98 at 28 days and p=0.11 at 90 days). Egger's test was not valid for one-year mortality (only five studies included). Two and ten studies were considered to be at high and uncertain risk of bias, respectively. The risk of bias assessment for each study is presented in supplementary tables 3 and 4.

Sensitivity and subgroup analyses

All but four studies categorised patients with non-severe alcoholic hepatitis by DF < 32; two used ABIC < 6.71,[3, 13] one, bilirubin < 85[39] and one, DF < 25.[43] A sensitivity analysis excluding these studies demonstrated a similar mortality proportion but with lower heterogeneity compared to the overall meta-analysis at 28 and 90 days of 7% (4-10%; I^2=54%; p=0.009) and 8% (4-12%; I^2=56%; p=0.007), respectively. Sensitivity analysis for 1-year mortality proportion was not performed due to the small number of studies after two were excluded.

Seven studies required histological confirmation of alcoholic hepatitis for inclusion of participants, while 12 used clinical features alone and six, clinical features with histology "where available", which occurred in 3-58% of participants (supplementary table 1). Nine studies met the NIAAA criteria for studies in alcoholic hepatitis,[9] seven by clinical diagnosis and histological confirmation of "definite" alcoholic hepatitis and two by clinical criteria for "probable" alcoholic hepatitis. A further four studies met similar criteria with the lower bilirubin threshold of 35 µmol/L and three studies required a bilirubin > 80 µmol/L for inclusion. Estimated mortality in studies using histological versus clinical entry criteria were similar at day 28 (6% [3-9%; 3 studies] versus 6% [2-10%; I^2=73%; p<0.01; 14 studies]) and day 90 (5% [1-12%; I^2=67%; p=0.01; 6 studies] versus 8% [4-13%; I^2=61%; p=0.01; 9 studies]). Both analyses demonstrated substantial heterogeneity. This subgroup analysis was not performed for 1-year mortality proportion due to the small number of studies in each group. Subgroup analysis of the nine studies that met NIAAA selection criteria versus other studies did not reveal differences in estimated mortality at either 28 or 90 days. At 28 days

estimated mortality of NIAAA conforming studies was 3% (0-8%; I^2=62%; p=0.02) compared to 8% (4-13%; I^2=58%; p=0.01) in other studies. At 90 days estimated mortality of NIAAA conforming studies was 6% (1-13%; I^2=70%; p=0.01) compared to 7% (3-12%; I^2=62%; p=0.01) in other studies. This subgroup analysis was not repeated for 1-year mortality due to the small number of studies.

Prospective versus retrospective study designs showed similar mortality proportions between groups. At 28 days, mortality proportion was 1% (0-7%; I^2=62%; p=0.02) for six prospective studies and 8% (5-12%; I^2=46%; p=0.05) for 11 retrospective studies. At 90 days, mortality proportion was 5% (1-12%; I^2=69%; p<0.01) in seven prospective studies and 9% (5-13%; I^2=54%; p=0.03) in eight retrospective studies.

There has been no significant difference in 28- or 90-day mortality between studies performed before or after 2010. At 28 days, studies performed during or before 2010 gave an estimated mortality of 4% (0-11%; I^2=79%; p<0.001) which was similar to those performed after 2010 at 7% (4-11%; I^2=36%; p=0.14; p=0.53 between groups). At 90 days, estimated mortality was similar in studies performed before 2010 and those performed after 2010 (6 and 7%, respectively; p=0.60).

Twenty studies were conducted in Caucasian, three in Asian and two in Hispanic populations. At 90 days, there was no difference in mortality proportion in studies conducted in predominantly Caucasian populations at 9% (5-14%; I^2=56%; p=0.02) and non-Caucasian populations at 5% (0-15%; I^2=57%; p=0.07). This subgroup analysis was not repeated for 28-day and 1-year mortality due to small numbers of studies in the non-Caucasian group.

Discussion

This is the first systematic review and meta-analysis conducted to evaluate the short- and medium-term mortality of patients with non-severe alcoholic hepatitis. Mortality at 28 days, 90 days and 1 year was 6%, 7% and 13% based on data from 993, 755 and 234 patients, respectively. Short-term mortality is higher than would be expected from Maddrey's original RCT, which reported no mortality in this group of patients. This 6% 28-day mortality rate is comparable to other acute conditions recognised for their mortality risk such as acute myocardial infarction with 30-day mortality of 6.2% in the USA[53] and community acquired pneumonia with 30-day mortality of 4.0% in Western Europe.[54] It is also higher than that for compensated cirrhosis, which has 5% 1-year mortality and is approaching that of Child Pugh B cirrhosis with 20% 1-year mortality.[55] However, it is important to note that up to 20% of patients with alcoholic hepatitis do not have established cirrhosis,[56] suggesting that the acute inflammatory process of alcoholic hepatitis itself contributes to increased risk of mortality. The limited data available from three studies confirm that the majority of deaths from non-severe alcoholic hepatitis are liver- or sepsis-related.

In comparison to severe alcoholic hepatitis with 28-day mortality of 19%[20] and 1-year mortality of more than 50%,[21] outcome is undoubtedly better in patients with non-severe alcoholic hepatitis. However, 13% 1-year mortality is significant and should become the focus of future research. Clear characterisation of both the patients and the condition will improve our understanding of the natural history of non-severe alcoholic hepatitis and the factors associated with poor outcome. Patients with non-severe alcoholic hepatitis should not be automatically excluded from future clinical trials. Indeed, as a trial population, this patient group offers an advantage to studying in its own right as patients have less severe liver dysfunction, making drug trials safer to conduct and the incidence of non-severe

alcoholic hepatitis is likely to be higher than the severe form. Interventional clinical trials are called for to improve survival of patients with non-severe alcoholic hepatitis.

Eligible studies were of variable design and quality and several have been reported in abstract form only. The primary analyses all had substantial heterogeneity reflecting the differences in study design, inclusion criteria or definition of non-severe alcoholic hepatitis. There was a large proportion of single centre retrospective observational studies (9/25), and many of the studies (12/25) were evaluated to be of uncertain or high risk of bias. However, subgroup analysis by study design (prospective versus retrospective) did not reveal any significant difference in survival proportions at 28 or 90 days.

We acknowledge the challenges in making a definitive diagnosis of alcoholic hepatitis and in differentiating non-severe alcoholic hepatitis from decompensated chronic alcohol-related liver disease solely by clinical features. Seven studies required histological confirmation of alcoholic hepatitis and met NIAAA criteria[9] for “definite” alcoholic hepatitis and a further two applied stringent clinical criteria to allow diagnosis of “probable” alcoholic hepatitis.[9] However, most studies were conducted prior to the publication of these criteria, which have now become widely adopted in clinical trials. To test whether the method of diagnosis of alcoholic hepatitis influenced the result of the meta-analysis, we performed a subgroup analysis comparing studies with histological versus clinical entry criteria as well as NIAAA criteria conforming and non-conforming studies, which both demonstrated similar mortality at 28 and 90 days. We are therefore confident that the mortality estimates do indeed relate to patients with non-severe alcoholic hepatitis.

There were limited data available on severity, measured either by DF or bilirubin level, which were only reported in five studies. Average DF ranged from 12 to 20 and average bilirubin from 26 to 140 µmol/L, although it is noted that lower values came from two studies requiring histological confirmation of the diagnosis. Despite such a range of severity, all studies only

included hospitalised patients with a prolonged history of heavy alcohol consumption, which remains a relevant group of patients in current clinical practice. However, both the wide spectrum of disease and differing patient selection criteria for each study limit the generalisability of this meta-analysis. These findings emphasise the need for a prospective study to collect detailed information on the characteristics and outcomes of patients with non-severe alcoholic hepatitis defined by stringent criteria such as those of the NIAAA.[9] This would also provide the opportunity to develop tools to improve the accuracy of scoring systems to predict mortality in patients with non-severe alcoholic hepatitis.

Early mortality rates, at both 28 and 90 days, reported in older studies (pre-2010) were similar to more recent studies. This concurs with a meta-analysis of mortality in all patients with alcoholic hepatitis, which did not show a change in 28- or 180-day mortality over time.[57] Despite improvements in the management of acutely unwell patients over the last four decades, this steady rate of mortality over time emphasises the need to concentrate attention on patients with non-severe alcoholic hepatitis to develop methods to improve their outcome.

Twenty studies were conducted in predominantly Caucasian populations and five in Asian or Hispanic populations but individual studies did not report survival outcome by ethnicity. Subgroup analysis by ethnicity did not demonstrate differences in survival proportions at 90 days. However, the meta-analysis findings have limited applicability to non-Caucasian populations.

Several different definitions of non-severe alcoholic hepatitis were applied in the included studies but DF < 32 was most commonly used (20/25). A sensitivity analysis excluding other definitions did not show any differences in the proportion surviving at 28 and 90 days. Only five studies with a total of 234 patients provided data on 1-year survival using three different definitions of non-severe alcoholic hepatitis making this meta-analysis less robust.

Only six out of 25 eligible studies reported information on patient characteristics. Thus, multivariable meta-regression was not appropriate. Selection bias is likely as at least three studies included only male subjects.[39, 43, 50]

Given the clinical and research emphasis on severe alcoholic hepatitis only, patient selection bias and reporting bias are likely. All 13 retrospective observational studies included patients identified through hospital diagnosis coding or histopathology results, which are both susceptible to excluding less severe forms of alcoholic hepatitis. Of the 25 eligible studies, only two studies (one prospective RCT[45] and one retrospective observational study in abstract form only),[37] focused solely on non-severe alcoholic hepatitis.

Conclusion

This systematic review and meta-analysis demonstrates that “non-severe” alcoholic hepatitis is poorly named and challenges the assumption that it is a benign condition. “Moderate” alcoholic hepatitis is a more apt descriptor. The significant burden of mortality, which has not improved over time, of 6% within 28 days and 13% at one year needs to be addressed. This systematic review has highlighted the paucity of high quality studies dedicated to this patient group. Consistent with a recent expert consensus statement,[10] we recommend further studies in a well-defined group of patients with non-severe alcoholic hepatitis to determine patient characteristics, long-term outcome and cause of death. This group of patients should become the focus of renewed research effort to develop strategies to improve their outcome.

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Figure legends

Figure 1. Results from literature search for studies relating to non-severe alcoholic hepatitis published prior to July 2018.

Figure 2. Forest plot of 28-day mortality of patients with non-severe alcoholic hepatitis showing estimated mortality, 95% confidence intervals (CI) and contribution to meta-analysis (% weight).

Figure 3. Forest plot of 90-day mortality of patients with non-severe alcoholic hepatitis showing estimated mortality, 95% confidence intervals (CI) and contribution to meta-analysis (% weight).

Figure 4. Forest plot of 1-year mortality of patients with non-severe alcoholic hepatitis showing estimated mortality, 95% confidence intervals (CI) and contribution to meta-analysis (% weight).